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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,428	07/16/2003	Dieter Heindl	21329-US	8931

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,428	HEINDL ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-20* is/are pending in the application.

4a) Of the above claim(s) *21-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 15-20 in the reply filed on October 4, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Preliminary Amendment

2. Applicant canceled claims 1-14 in preliminary amendment filed on July 6, 2003. However, there are no claims 1-14 in this instant application. Please clarify.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in European on July 23, 2002. It is noted, however, that applicant has not filed a certified copy of this foreign application as required by 35 U.S.C. 119(b).

Specification

4. The disclosure is objected to because of the following informalities: there are Figures 1A, 1B, 2A, and 2B in this instant application. However, Brief Description of the Figures only describes Figures 1 and 2.

Appropriate correction is required.

Claim Objections

5. Claim 1 is objected to because of the following informalities: Note that "FRET" is an abbreviation. This abbreviation can only be used after whole name of the abbreviation appears once.

6. Claims 16 and 18 are objected to because of the following informalities: "quenching fluorescence emission" in lines 2 and 3 should be "quenching fluorescence" because quenching is related to alteration of fluorescence density and is not related to alternative of fluorescence emission.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synthesizing an oligonucleotide with a fluorescent donor and a fluorescent acceptor wherein the fluorescent donor and the fluorescent acceptor are located on different residues of the oligonucleotide, does not reasonably provide enablement for synthesizing an oligonucleotide with a fluorescent donor and a fluorescent acceptor wherein the fluorescent donor and the fluorescent acceptor are located on the same residue of the oligonucleotide. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 15 and 17 are not included in the rejection since these claims are directed to an oligonucleotide with a fluorescent donor and a fluorescent acceptor wherein the fluorescent donor and the fluorescent acceptor are located on different residues of the oligonucleotide which are enabling in view of Mathies *et al.*, (US Patent No. 6,028,190, published on February 22, 2000) (see below).

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

Claims 16 and 18 require that said first oligonucleotide carrying the donor fluorescent entity also carries said second entity which is capable of quenching fluorescence of said donor fluorescent entity wherein the fluorescent donor and the fluorescent acceptor are located on the same residue of said first oligonucleotide. It is well known that an oligonucleotide with a fluorescent donor and a fluorescent acceptor, wherein the fluorescent donor and the fluorescent acceptor are located on different residues of the oligonucleotide, can be synthesized. However, the specification does not show that an oligonucleotide with a fluorescent donor and a

fluorescent acceptor, wherein the fluorescent donor and the fluorescent acceptor are located on the same residue of the oligonucleotide, can be synthesized. Furthermore, the searches for prior art cannot find an oligonucleotide with a fluorescent donor and a fluorescent acceptor wherein the fluorescent donor and the fluorescent acceptor are located on the same residue of the oligonucleotide. It is also unclear whether the fluorescent acceptor that locates on the same residue which the fluorescent donor is attached to on the oligonucleotide is capable of quenching fluorescence of said donor fluorescent entity.

Therefore, with these unpredictable factors, the skilled artisan will have no way to predict the experimental results. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed. These undue experimentations at least include to test whether an oligonucleotide with a fluorescent donor and a fluorescent acceptor, wherein the fluorescent donor and the fluorescent acceptor are located on the same residue of the oligonucleotide, can be synthesized.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 15 is rejected as vague and indefinite because it is unclear that "FRET donor entity" in line 2 and "the donor fluorescent entity" in line 3 are identical or not. If "FRET donor

entity" in line 2 and "the donor fluorescent entity" in line 3 are not identical, "the donor fluorescent entity" lacks antecedent basis. Please clarify.

12. Claim 17 is rejected as vague and indefinite. Since a first oligonucleotide and a third oligonucleotide can carry a FRET donor entity, it is unclear that "the oligonucleotide carrying the FRET donor entity" in line 6 means a first oligonucleotide or means a third oligonucleotide. Please clarify.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 15, 17, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathies *et al.*, (US Patent No. 6,028,190, published on February 22, 2000).

Mathies *et al.*, teach probes labeled with energy transfer coupled dyes.

Regarding claim 15, since Mathies *et al.*, teach that each of two primers, F2R and F6R, is labeled with a fluorescence donor (ie., FAM) and a fluorescence acceptor (ie., ROX) (see Figure 22 and column 10, right column), Mathies *et al.*, disclose that first oligonucleotide (ie., F2R) carrying a FRET donor entity (ie., FAM) and a second oligonucleotide (ie., F6R) carrying a FRET acceptor entity (ie., ROX) wherein the oligonucleotide carrying the donor fluorescent entity (ie., F2R) carries at least one second entity (ie., ROX), said second entity being a

compound (ie., ROX) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) as recited in claim 15.

Regarding claim 17, Mathies *et al.*, teach that each of two primers, F2R and F6R, is labeled with a fluorescence donor (ie., FAM) and a fluorescence acceptor (ie., ROX) (see Figure 22 and column 10, right column) and F2R and F6R are THO1-A and THO1-B that are used as PCR primers to amplify THO1 loci (see columns 18-20), Mathies *et al.*, disclose a first oligonucleotide and a second oligonucleotide (ie., F2R and F6R or THO1-A and THO1-B) capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction as recited in claim 17. Since PCR product amplified using F2R and F6R must carry a fluorescence donor (ie., FAM) and a fluorescence acceptor (ie., ROX), Mathies *et al.*, disclose further characterized in that said first oligonucleotide (ie., F2R) and a third oligonucleotide (ie., the PCR product amplified using F2R and F6R) are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity (ie., FAM) and a FRET acceptor entity (ie., ROX) wherein the oligonucleotide (ie., F2R) carrying the FRET donor entity (ie., FAM) carries at least one second entity (ie., ROX), said second entity being a compound (ie., ROX) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) as recited in claim 17.

Regarding claim 19, since Mathies *et al.*, teach a genomic DNA template used for PCR (see column 18) and all limitations recited in claim 15, Mathies *et al.*, disclose a composition comprising a nucleic acid sample (ie., a genomic DNA template used for PCR) and a pair of hybridization probes (ie., F2R and F6R) according to claim 15 as recited in claim 19.

Therefore, Mathies *et al.*, teach all limitations recited in claims 15, 17, and 19.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies *et al.*, (2000) as applied to claims 15, 17, and 19 above, and further in view of Stratagene catalog (page 39, 1988).

The teachings of Mathies *et al.*, have been summarized previously, *supra.* As shown the rejection under 35 U.S.C 102, Mathies *et al.*, teach a pair of hybridization probes according to claim 15 as recited in claim 20. Since Mathies *et al.*, also teach Taq DNA polymerase and dNTPs in the PCR reaction (see column 18), Mathies *et al.*, disclose at least one other component as recited in claim 20.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a pair of probes and at least one other component such as a template dependent nucleic acid polymerase (ie., Taq DNA polymerase) taught by Mathies *et al.*, into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "[E]ach kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically

for a defined set of experiments. 2) The other service provided in a kit is quality control" (page 39, column 1).

Conclusion

17. No claim is allowed.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
October 29, 2004

FRANK LU
PATENT EXAMINER